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10/510,040	06/21/2005	Thomas Schmehl	080618-0576	4643

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EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,040	SCHMEHL ET AL.	
	Examiner	Art Unit	
	ISAAC SHOMER	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-49* is/are pending in the application.

4a) Of the above claim(s) *14-16,19,20 and 27-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-13, 17-18, 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *21 June 2005, 29 July 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The examiner clarifies that claims 30-49 are drawn to Group II.

Applicant's election with traverse of Group I, claims 11-29 in the reply filed on 29 April 2009 is acknowledged. The traversal is on the ground(s) that the examiner has not provided adequate grounds for search burden. This is not found persuasive because the instant application has been submitted under 35 U.S.C. 371. Therefore, lack of unity practice applies to the instant application (as opposed to US restriction practice), and search burden is not a relevant criterion in lack of unity practice.

The requirement is still deemed proper and is therefore made FINAL.

Claims 30-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 29 April 2009.

Applicant's election with traverse of the species sphingomyelin (as of the third component of the liposome), nebulizer (as of the method of administering the liposomal composition) and a drug as the active agent, in the reply filed on 29 April 2009 is acknowledged. The traversal is on the ground(s) that the examiner has not provided adequate grounds for search burden. This is not found persuasive because the instant application has been submitted under 35 U.S.C. 371. Therefore, lack of unity practice

applies to the instant application (as opposed to US restriction practice), and search burden is not a relevant criterion in lack of unity practice.

The requirement is still deemed proper and is therefore made FINAL.

Claims 15-16, 19-20, 27, and 28-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 29 April 2009. Claims 15-16 and 19 are withdrawn pursuant to nonelected species of the third component of the liposome. Claim 27 is withdrawn pursuant to a non-elected species of active agent, and claims 20 and 28-29 are withdrawn pursuant to a non-elected species of administration of the liposomal composition.

Claims 11-14, 17-18 and 21-26 are under substantive examination.

Claim Rejections - 35 USC § 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-14, 17-18 and 21-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 depends upon itself. Therefore, its scope is indefinite. As claims 22-24 depend upon indefinite claim 21, said claims have an indeterminate scope as well. For

the purpose of examination under art, indefinite claims 21-24 will be examined as of they depend upon claim 11.

Claim 11 recites the limitation “to a subject in need thereof.” As the specification does not define "a subject in need thereof," this phrase is indefinite, as one of ordinary skill in the art at the time the invention was made would not have been aware of which subjects are in need of the instantly claimed method of administration. For the purpose of examination, the indefinite limitation "a subject in need thereof," will be interpreted as any human or animal subject to whom the preparation is administered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 26 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See, e.g., In re Wilder, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did ‘little more than outline goals

appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.')

Mere indistinct terms (such as "derivative" used in instant claim 26), however, may not suffice to meet the written description requirement. This is particularly true when a compound is claimed in purely functional terms. See Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886 (CAFC 2004) at 1892, stating:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice.... The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

Conversely, a description of a chemical genus will usually comprise a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. See Univ. of Calf. V. Eli Lilly, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under Section 112, ¶ 1, by showing the enablement of a representative number of species within the genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. *If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus*. See MPEP 2163. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the

method of making the claimed invention. Disclosure of any *combination of such identifying characteristics that distinguish the claimed invention from other materials* and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP 2163.

Here, the specification does not provide a reasonably representative disclosure of useful prostacyclin derivatives generally, a potentially huge genus inclusive of many different compounds having widely divergent structures and functions. Specifically, the specification discloses only the phrase “prostacyclin and derivatives thereof" at page 4 lines 10-15, and this is not viewed as being reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purpose of examination under art, indefinite claims 21-24 will be examined as of they depend upon claim 11.

Claims 11-13, 17-18, and 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mihalko et al. (US Patent 5,340,587) in view of Webb et al. (US Patent 5,814,335) in view of Hunt et al (Am J Respir Crit Care Med 2000; 161: 694-699).

Mihalko teaches a method of treating bronchial constriction, comprising providing a liposome comprising a beta 2-andrenoreceptor agonist drug in liposome encapsulated form, aerosolizing, in a form suitable for inhalation (page 22, lines 52-59). With regards to the bronchial constriction, the patent teaches that disease associated with bronchial constriction include, but are not limited to, asthma (column 1, lines 40-42). With regards

to the liposome, the patent teaches that liposomes include, but are not limited to, those comprising DPPC and cholesterol (column 16, Table 4). In particular, the patent teaches a liposome comprising DPPC and cholesterol in a molar ratio or 6 to 4 (column 16, Table 4). With regards to the administration, the patent teaches that the drug aerosols are administered by Pulmosonic nebulizer inserted between a respirator and a solenoid-operated valve at the tracheal cannula (see for example column 21, lines 50-52).

Mihalko does not teach that the liposome further comprises sphingomyelin.

Webb teaches that liposomes composed of sphingomyelin and cholesterol are more stable to acid hydrolysis than those comprised of phosphatidylcholine and cholesterol (column 10 Example 1, as well as Figure 1). Example 1 indicates that at pH 4.0, liposomes comprising sphingomyelin and cholesterol were significantly less susceptible to acid hydrolysis than those comprising phosphatidylcholine and cholesterol.

Hunt shows, on page 695, left column, Figure 1, that the components of lungs afflicted by asthma are more acidic than those of healthy lungs. This indicates that acid resistance is most necessary among those patients most likely to require pulmonary treatment due to asthma.

It would have been prima facie obvious for one of ordinary skill in the art to have modified the liposome used in the method taught by Mihalko et al. to further include sphingomyelin in view of the teachings of Webb and Hunt. One would have been

motivated to do so because as taught by Webb, sphinogomyelin increases the hydrolysis stability of cholesterol containing liposomes to acid hydrolysis; and further, as taught by Hunt et al. components of the lung afflicted with asthma are more acidic than those of healthy lung. Thus, one of skill in the art would have a reasonable expectation of success that by modifying the liposome used in the method taught by MIhalko et al. to further include sphingomyelin in view of the teachings of Webb and Hunt, one would achieve a liposome having increased staiblity to acid hydrolysis for the treatment of diseases associated with bronchial constriction.

The combination cited above does not explicitly teach that sphingomyelin is present at 2% to 8% by mass, as of claim 18, or that the molar ratio of DPPC to cholesterol of between 7:3 and 7:4, as of claim 16.

However, it would have been prima facie obvious for one of ordinary skill in the art to have optimized the concentration of sphingomyelin and DPPC to cholesterol in view of the teachings of the combination of Mihalko and Webb. One would have been motivated to do so because the courts have held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. Thus, one of skill in the art would have a reasonable expectation that by optimizing the concentration of sphingomyelin and DPPC to cholesterol in view of the teachings of the combination of Mihalko and Webb, one would achieve a liposome which retains it acid resistant properties and as well as a slow release of the drug.

Mihalko in view of Webb do not teach that 50% to 80% of the liposomes remain intact, as of claim 13.

It would have been prima facie obvious for one of ordinary skill in the art to have optimized the method of administration and the liposome composition to be administered such that 50% to 80% of the liposomes remain intact after administration. One would have been motivated to do so because the courts have held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. Thus, one of skill in the art would have a reasonable expectation that optimizing the components of an intact liposome would cause slower and more uniform drug delivery, resulting in a longer duration of treatment.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mihalko et al. (US Patent 5,340,587) in view of Webb et al. (US Patent 5,814,335) in view of Hunt et al (Am J Respir Crit Care Med 2000; 161: 694-699), as applied to claim 25 above, and further in view of Morton Jr. et al. (US Patent 4.732,914)

Mihalko in view of Webb and Hunt teach a method of pulmonary administration of a liposomal composition comprising DPPC, cholesterol, and sphingomyelin, wherein a beta 2-andrenoreceptor agonist drug (an active agent) is encapsulated into said liposome.

Mihalko in view of Webb do not teach the administration of prostacyclin to the lungs, wherein prostacyclin is encapsulated in a liposome, as of claim 26.

Morton Jr. teaches prostacyclins and derivatives thereof, and methods of preparing thereof, as of Morton Jr., column 1 lines 8-14. The examiner notes the examples, wherein prostacyclin derivatives are prepared, and charts to which Morton Jr. refers. Morton Jr., column 4 lines 19-30, further teaches that prostacyclins are useful in the treatment of asthma, as prostacyclins act as both bronchodialators, and inhibit histamine and SRS-A, thereby controlling spasms and facilitating breathing.

It would have been prima facie obvious for one of ordinary skill in the art to have encapsulated a prostacyclin into the liposome made by the combination of Mihalko in view of Webb and Hunt. Morton Jr., column 4 lines 19-30, further teaches that prostacyclins are useful in the treatment of asthma, and Mihalko in view of Webb and Hunt show that an acid-resistant liposome is useful in the delivery of drugs to asthmatic patients due to the increased acidity seen in said patients. Therefore, the liposomes of Mihalko Webb and Hunt, as well as the active agents of Morton Jr. have an additive effect in the treatment of asthma. The examiner reference" In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980), which renders obvious the combination of two separate elements used for the same purpose.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/I. S./
Examiner, Art Unit 1612

/Brandon J Fetterolf/

Primary Examiner, Art Unit 1642